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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,533	01/15/2004	Marcus Keep	0030-0208P	4570

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,533	KEEP ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/15/2004 and 01/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-17 are pending.

Response to election of species requirements applicant elected as cyclophilin ligand, and dosage range of 0.001-50 mg/kg for parenteral administration. Claims 1-17 read on the elected invention and are addressed to the extent they reads on the elected species.

Priority

This application is a continuation of application Serial No. 09/787,861, which was filed on June 14, 2001. Serial No. 09/787,861 was a U.S. national phase application of PCTFUS98/20040, which was filed on September 23, 1998.

Information Disclosure Statement

Applicants' Information Disclosure Statements filed 01/15/2004 and 01/10/2005 have been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cyclosporin A in the presence of means of purposeful disruption of the blood-brain barrier, does not reasonably provide enablement for either cyclosporin derivatives, metabolites, variants as claimed, as well as administration in the absence of means of purposeful disruption of the blood-brain barrier

First, with respect to administering cyclophilin ligand which is able to cross blood-brain barrier, WO 96/22104 teaches that cyclosporins do not normally cross the blood-brain barrier and specifically point out that neuroprotective effct of cyclosporins can be achieved only in situation wherein the blood-brain barrier has been opened, disrupted, obviated by other means. (see p. 5, paragraphs 3,5; p. 6, second paragraph). For example paragraph bridging pages 5-6 teaches that

> Animals that received cyclosporin A but without opening the blood-brain barrier had more than 80% cell death. Animals that received cyclosporin A with the opening of the blood-brain barrier had only 11% cell death

Instant specification offers all the same cyclophilin agents as in WO 96/22104 (see art rejection below) but is not offering guidance on how to achieve neuroprotective effect in the absence of means of purposeful disruption of the blood-brain barrier. Specification does teach that Included in the invention is administration of the treatment medication via any means with purposeful disruption of the blood-brain barrier (p. 8, paragraph 2). As for working examples, instead of working examples, specification offers prophetic examples of typical situations where neuroradioprotection in accordance with this invention "can be used" (pages 13-15). No actual results are provided.

Therefore, insufficient guidance exist in the specification to enable a person of skill in the art to practice the invention in the absence of means of purposeful disruption of the blood-brain barrier without the need for undue experimentation.

With respect to cyclosporin derivatives, metabolites, variants, specification lists an extensive list of cyclosporin derivatives, metabolites, variants, fragments, etc (p. 3, last two paragraphs). The teaching in the specification is limited to cyclosporin itself (in fact, there are no working example of effect of cyclosporin either; the existing examples are rather illustration of potential uses). It is not clear what core structure is needed for a cyclosporin derivative, metabolite, variant to be effective as claimed. For example, does it require cyclic structure of cyclosporin to be intact? Further, the claims require that cyclophilin ligand is able to cross the blood-brain barrier but does not provide

guidance as to what core structure elements are required for a cyclosporin derivative, metabolite, variant to be capable of this functional limitation.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9-14 are rejected under 35 U.S.C. 102(b) as anticipated by Elmer et al (WO 96/22104).

The instant claims are drawn to method for reducing neuron death from ionizing radiation by administration to mammals a cyclophilin ligand (cyclosporin A is elected species) before administering radiation.

Elmer et al (WO 96/22104) disclose neuropreventive use of neuroimmunophIIIn ligands like cyclosporins, especially cyclosporin A, its derivatives, metabolites, variants, or salts thereof for the prevention of mammal neuron damage or death caused by, e.g., radiation (page 4, paragraph 3). The neuroimmunophIIIn ligand can be administered

before, or simultaneously with inflicting neuron damage (see page 5, paragraph 2; claim 2). The neuroimmunophllln ligand can be administered by several routes like Intravenous, intraarterial, parenteral, Intra parenchymal, via cerebrospinal fluid spaces, intra ventricular fluid spaces, or by application into digestive, respiratory, genitourinary systems or to the skin (see page 8, bottom). Amounts of from 0.0001 mg to 50 mg/kg, or preferably 0.001 to 25 mg/kg, of body weight per day for parenteral administration, and 0.001 to 100 mg/kg, preferably 0.01 to 60mg/kg, of body weight per day for enteral administration, can be given to achieve neuroprotection.

Claims 6-8,15-17 are rejected under 35 U.S.C. 103(a) as obvious over WO 96/22104 in view of Bradley et al. and Pellmar et al.

With respect to claims 6-8,15-17 if there are any differences between Applicant's claimed method and that of the prior art, the differences would be appear minor in nature. Although the prior art does not teach treatment of cancer patients, it teaches neuroprotective effect of neurons subjected to such treatment as radiation (p.4, paragraph 3).

Pellmar et al. teach that radiation, γ radiation in particular, causes a substantial damage to neurones, at the level of synaptic and postsynaptic functions. See pages 256-257.

Bradley et al. teach that radiation causes neuronal damage and neuronal death. See pages 345,348.

It would have been *prima facie* obvious at the time the invention was made to be motivated to use cyclosporin to treat neuronal damage and cell death caused by radiation because Elmer et al (WO 96/22104) disclose neuroprotective effects in preventing damage occurring during radiation and Pellmar and Bradley teach that radiation causes a substantial damage to neurons. Thus, one would expect that cyclosporin would be effective in reducing neuron death caused by radiation. A person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Borin, Ph.D.

Primary Examiner

Art Unit 1631

mlb